

Editorial

Radiation induced coronary heart disease

The heart was considered to be a relatively radioresistant organ by radiotherapists in the 1950s when data on normal tissue tolerance were sparse. Radiation techniques evolved with field arrangements that resulted in the maximum dose being received by the anterior mediastinal structures with a progressive fall posteriorly, which afforded maximal sparing of the dose to the spinal cord. The ensuing reports of cardiac complications included pericardial effusion, constriction, and tamponade¹ which were radiation induced.

Evidence for radiation induced coronary artery disease

The possibility of radiation induced coronary artery disease is much more difficult to demonstrate. The disease pattern may not differ from that of ischaemic heart disease, though ischaemic heart disease usually affects an older age group than, for example, patients with Hodgkin's disease who have received mediastinal irradiation.

In 1957 Pearson first reported that intimal proliferation secondary to chest wall irradiation might have caused myocardial infarction in two patients with breast cancer who received chest wall irradiation. In 1960 Caterall and Evans reported the development of T wave changes on serial electrocardiography after similar treatment.³

More than 25 isolated case reports followed. Interpretation is, however, difficult because many patients had at least one recognised risk factor for ischaemic heart disease, the interval since radiation varied, the radiation details were often incomplete, and histological information was only available in a few cases. However, the young age of many of the patients; the predilection for involvement of the proximal right main and the left anterior descending coronary arteries,⁴ which lie anteriorly in the mediastinum and therefore receive the maximum radiation dose; and the presence of intimal fibrosis in histological specimens⁴ are all circumstantial evidence for premature coronary artery disease.

Mechanisms

Intimal fibrosis and accelerated atherogenesis are the two postulated pathological mechanisms of radiation induced coronary artery disease. Amronim and Solomon used a 2 × 2 factorial design to study the effects of a high cholesterol diet and radiation in rabbits.⁵ When both factors were combined considerable atherosclerosis developed whereas radiation alone produced only rare lesions. In contrast, studies of a low cholesterol diet in dogs in which other risk factors were excluded showed severe intimal thickening and fibrous plaque formation as early as two months after neutron irradiation. Similar, but less extensive changes were found after photon irradiation, whereas no lesions were found in any of the controls.⁶

Brosius *et al* performed a detailed pathological study of coronary arteries after irradiation.⁴ Sixteen patients aged less than 35 who had received at least 3500 cGy (rad) to the heart were studied at necropsy. The radiation techniques used delivered a higher dose from the anterior radiation field and thus increased the dose received by the anterior heart (median 5248 cGy) while the posterior heart received a lower dose (median 4000 cGy). Thirteen patients had Hodgkin's disease, one patient had non-Hodgkin's lymphoma, and two patients had carcinoid tumours. None had cardiac symptoms although five had physical signs of pericardial constriction. Comparisons were made with ten age-matched controls. Of nearly 500 segments of coronary arteries studied, stenosis of >75% was found in 6% of the irradiated patients compared with 0.2% of controls. In the irradiated patients there was also a highly statistically significant increase in proximal stenosis of the right main and left anterior descending coronary arteries and, histologically, of partial medial replacement by fibrous tissue and adventitial fibrosis.

Studies

In studies of large cohorts of patients who received mediastinal irradiation for early stage Hodgkin's disease the estimated crude incidence for non-fatal myocardial infarction and cardiac mortality was 0-3%.⁷⁻¹¹ Actuarial analysis reveals a higher incidence. Cosset *et al* treated 499 patients with mantle radiotherapy and found a 3.9% actuarial 10 year incidence of non-fatal myocardial infarction whereas in a parallel group of 138 patients receiving chemotherapy alone there were no cases of myocardial infarction.⁸ Similarly, in the pooled European Organisation of Research and Treatment of Cancer trials of over 1000 patients the reported incidence of myocardial infarction was 4.6% at 15 years and cardiac mortality was 6.7% at 20 years. The standardised mortality ratio was 10.17, and this increased with time, peaking 3-11 years after treatment.⁸ However, none of the reported studies was randomised with respect to irradiation. Also the radiation techniques used in these studies include factors that would not be considered acceptable today.

The most powerful evidence suggesting radiation induced coronary artery disease comes from the long-term follow up of large studies of patients with early stage breast cancer randomised with respect to chest wall irradiation after mastectomy.¹²⁻¹⁴ Cuzick *et al* in an overview of 7941 patients in ten trials¹⁵ found that when follow up exceeded 10 years, a highly statistically significant increase in mortality was seen in the irradiated group. There was an excess of 48 deaths in the irradiated group after 10 years, when approximately 1400 patients were alive in each group. This overview has been criticised because it included trials in which the randomisation process is not now regarded as being statistically free of bias and could have accounted for most of the excess deaths. The cause of death was also not studied.

Is there any evidence to suggest excess cardiac deaths

in any randomised breast cancer trials? Haybittle *et al* reported a detailed analysis of the causes of death in the large multicentre national Cancer Research Campaign trial that randomised patients with respect to chest wall irradiation after mastectomy.¹⁶ This later analysis of the trial was performed when the minimum follow up period exceeded 13 years. They found an excess cardiac mortality in the radiotherapy group as a whole (relative risk of 1.65 (95% confidence interval 1.05 to 2.58)). Subset analysis suggested that the risk was greatest when left-sided tumours were treated with low energy (orthovoltage) x rays. Both of these factors significantly increase the cardiac dose. Host *et al* in a more recent randomised trial of megavoltage x rays and a total dose of 5000 cGy with increased daily fraction doses (250 cGy) reported that the number of deaths from myocardial infarction was significantly increased in those irradiated patients with stage I breast cancer.¹³ In this study the internal mammary lymph nodes were irradiated by a direct anterior field with the anterior heart receiving almost the full dose. Neither of these factors would be regarded as standard practice today.

Changes in techniques

All aspects of radiotherapy have changed considerably over the past three decades. Changes include the use of higher energy (megavoltage) beams, equal doses of irradiation from opposing treatment fields to avoid dose gradients, and the use of a low daily dose (fraction size). These improvements result in a more homogeneous and lower biological total dose. Additionally, the omission of routine irradiation of the internal mammary nodes in breast cancer and the use of sub-carinal lead shielding in mantle radiotherapy for Hodgkin's disease have significantly reduced the volume of the heart receiving irradiation.

Further refinements include the recognition of the importance of quality assurance programmes¹⁷ and more rigid radiotherapy guidelines and central review of treatment plans. These are being used in the current multicentre national pilot study of early stage Hodgkin's disease conducted by the British National Lymphoma Investigation.

There seems to be clear historical evidence of premature coronary artery disease in patients who have received curative doses of irradiation to the mediastinum or chest wall. However, the radiation quality, radiation tech-

niques, and dose fractionation used in all of the above studies would not be regarded as acceptable today. Further refinement of radiation techniques continues to reduce the radiation dose to the heart without compromising local tumour control. Meticulous reporting of cardiac events in all patients who have received mediastinal or chest wall irradiation by modern techniques may allow a future meta-analysis to determine whether late effects on the coronary arteries are a complication of the past.

DAVID SEBAG-MONTEFIORE

Department of Radiotherapy,
St Bartholomew's Hospital, London

HAROLD HOPE-STONE

The London Independent Hospital
and The Royal London Hospital

- 1 Cohn KE, Stewart JR, Fajardo LF, Hancock EW. Heart disease following radiation. *Medicine* 1967;46:281-98.
- 2 Pearson HES. Coronary occlusion following thoracic radiotherapy: 2 cases. *Proc R Soc Med* 1957;60:516.
- 3 Catterall M, Evans W. Myocardial injury from therapeutic irradiation. *Br Heart J* 1960;22:168.
- 4 Brosius FC, Waller BF, Roberts WC. Radiation heart disease: analysis of 16 young (aged 15-33 years) necropsy patients who received over 3500 rads to the heart. *Am J Med* 1981;70:519-30.
- 5 Amronin GD, Solomon RD. Production of arteriosclerosis in the rabbit: a quantitative assessment. *Arch Pathol* 1965;75:219-27.
- 6 Bradley EW, Zook BC, Casarett GW, Rogers CC. Coronary arteriosclerosis and atherosclerosis in fast neutron or photon irradiated dogs. *Int J Radiat Oncol Biol Phys* 1981;7:1103-8.
- 7 Carmel RJ, Kaplan HS. Mantle irradiation in Hodgkin's disease. An analysis of technique, tumour eradication and complications. *Cancer* 1976;37:2813-25.
- 8 Cosset JM, Henry-Amar M, Meerwaldt JH. Long term toxicity of early stages of Hodgkin's disease therapy: the EORTC experience. *Ann Oncol* 1991;2(suppl 2):77-82.
- 9 Boivin J-F, Hutchinson GB. Coronary heart disease mortality after irradiation for Hodgkin's disease. *Cancer* 1982;49:2470-5.
- 10 Hancock SL, Hoppe RT, Horning SJ, Rosenberg SA. Intercurrent death after Hodgkin's disease therapy in radiotherapy and adjuvant MOPP trials. *Ann Intern Med* 1988;109:183-9.
- 11 A Collaborative Study. Radiotherapy of stage I and II Hodgkin's disease. *Cancer* 1984;54:1928-42.
- 12 Jones JM, Ribeiro GG. Mortality patterns over 34 years of breast cancer patients in a clinical trial of post-operative radiotherapy. *Clin Radiol* 1989;40:204-8.
- 13 Host H, Brennhovd I, Loeb M. Post operative radiotherapy in breast cancer—long term results from the Oslo study. *Int J Radiat Oncol Biol Phys* 1986;12:727-32.
- 14 The Cancer Research Campaign Working Party. The Cancer Research Campaign (Kings/Cambridge) trial for early breast cancer. *Lancet* 1980;ii:55-60.
- 15 Cuzick J, Stewart H, Peto R, *et al*. Overview of randomised trials of post-operative adjuvant radiotherapy in breast cancer. *Cancer Treat Rep* 1987;71:15-29.
- 16 Haybittle JL, Brinkley D, Houghton J, A'Hearn RP, Baum M. Postoperative radiotherapy and late mortality: evidence from the Cancer Research Campaign trial for early breast cancer. *BMJ* 1989;298:1611-4.
- 17 Sebag-Montefiore D, Maher EJ, Young J, Vaughan Hudson G, Hanks G. Variation in mantle technique: implications for establishing priorities for quality assurance in clinical trials. *Radiation Oncol* 1992;23:144-9.